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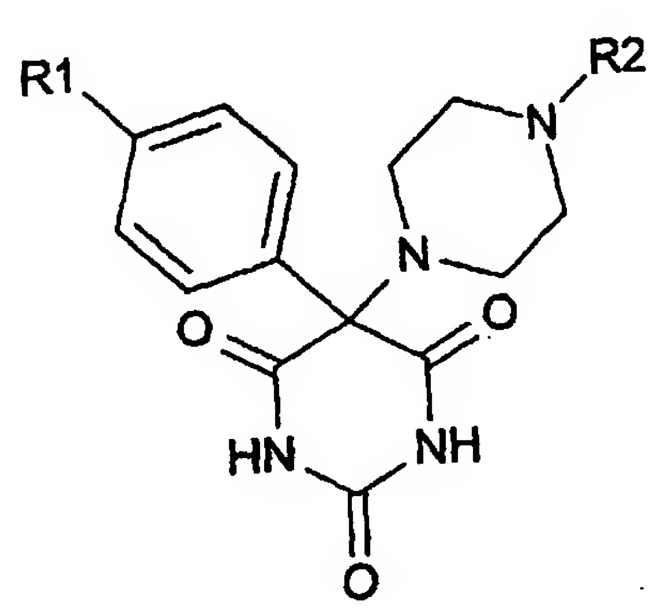
(54) Title: NEW PYRIMIDINE-2,4,6-TRIONE DERIVATIVES, PROCESSES FOR THEIR PRODUCTION AND PHARMACEUTICAL AGENTS CONTAINING THESE COMPOUNDS



(I)

(57) Abstract: Compounds of formula (I) in which R_1 represents a substituted or unsubstituted phenoxy, phenylthio, phenylsulfinyl, phenylsulfonyl, phenylamino or phenylmethyl residue, and R_2 represents an optionally substituted aryl or heteroaryl residue, with metallo-proteinase inhibitor activity.

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New Pyrimidine-2,4,6-trione derivatives, processes for their production and pharmaceutical agents containing these compounds

This invention relates to new derivatives of 5,5-disubstituted pyrimidine-2,4,6-triones. These compounds show a marked antitumor and antimetastatic activity

In normal tissue there is an equilibrium between synthesis and degradation. Extracellular matrix is degraded by proteinases which belong to at least three groups of matrix metalloproteinases. These are the collagenases, gelatinases and stromelysins. Normally there are specific inhibitors for these catabolic enzymes such as α_2 macroglobulines and TIMP (= tissue inhibitor of metalloproteinases (MMP)) so that an excessive degradation of extracellular matrix does not occur. Adamalysins are a related group of proteinases.
A prominent member of the adamalysins is TACE (TNF-α-converting enzyme).

At least 17 different and yet highly homologous MMP species have been characterized, including the interstitial fibroblast collagenase (MMP-1, HFC), the neutrophil collagenase (MMP-8, HNC), two gelatinases, stromelysins (such as HSL-1) and HPUMP (for a recent review, see Birkedal-Hansen, H., Moore, W.G.I., Bodden, M.K., Windsor, L.J., Birkedal-Hansen; B., DeCarlo, A., Engler, J.A., Critical Rev. Oral Biol.Med. (1993) 4, 197-250. These proteinases share a number of structural and functional features but differ somewhat in their substrate specificity. Only HNC and HFC are capable of cleaving type I, II and III native triple-helical collagens at a single bond with the production of fragments 3/4 and 1/4 of the native chain length. This lowers the collagen melting point and makes them accessible to further attack by other matrix degrading enzymes.

However, the uncontrolled excessive degradation of this matrix is a characteristic of many pathological states such as e.g. in the clinical picture of rheumatoid arthritis, osteoarthritis and multiple sclerosis, in the formation of tumor metastases, corneal ulceration, inflammatory diseases and invasion and in diseases of bone and teeth.

It can be assumed that the pathogenesis of these clinical pictures can be favourably influenced by the administration of matrix metalloproteinase inhibitors. In the meantime

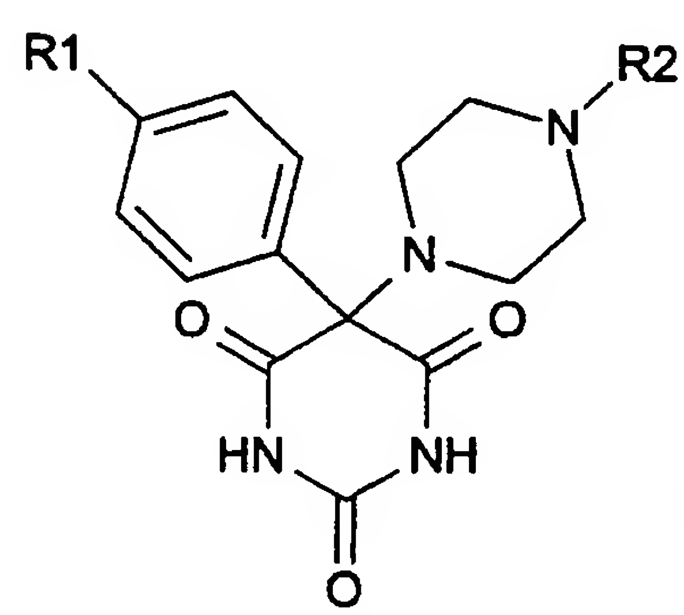
a number of compounds are known from the literature (see e.g. the review article of D.E. Levy, A.M. Ezrin Emerging Drugs 2, 205-230 (1997), M. Whittaker, P. Brown, Curr. Opin. Drug Discovery Dev. (1998), 1(2), 157-164. or are described in the patent literature, mainly with a hydroxamic acid residue, a thiol or phosphine group as a zinc binding group (see e.g. WO-A-9209563 by Glycomed, EP-A-497 192 by Hoffmann-LaRoche, WO-A-9005719 by British Biotechnology, EP-A-489 577 by Celltech, EP-A-320 118 by Beecham, US-A-459 5700 by Searle , WO 97/20824 by Agouron Pharmaceuticals , WO 96/15096 by Bayer Corporation among others).

Some of these compounds show a high activity as inhibitors of matrix metalloproteinases but their oral availability is very low. Also such compounds often show broad spectrum inhibition of metalloproteinases which may be associated to undesired side-effects and toxicity.

Pyrimidine-2,4,6-trione derivatives have been described in EP0869947 generically as inhibitors of matrix metalloproteinases. However, there is still a high need for new compounds having low toxicity, no side-effects and a marked inhibitory activity against metallo-proteinases, especially as candidates for a chronic treatment against tumor growth and metastasis.

It has now been found that the claimed new pyrimidine-2,4,6-trione derivatives have improved activity as matrix metallo-proteinase inhibitors over the compounds claimed in EP0869947 and also show good oral availability.

The present invention therefore concerns compounds of the general formula I



(I)

in which

R_1 represents a phenyl, phenoxy , phenylthio, phenylsulfinyl, phenylsulfonyl , phenylamino or phenylmethyl residue, wherein the phenyl moiety can be substituted by one or more halogen atoms, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkyl, cyano, or nitro groups, preferred are substitutions in para and/or meta position by one to two substituents.

R_2 represents an optionally substituted aryl or hetaryl group,

The present invention also encompasses pharmaceutically acceptable salts or prodrugs of the compounds of formula I as well as the use of these compounds to produce pharmaceutical agents.

The aryl group listed in case of R2 consists of a phenyl ring .The hetaryl group is understood as a cyclic unsaturated or saturated ring system consisting of 5 to 7 ring atoms which can be selected from one or more carbon, nitrogen, oxygen or sulfur atoms. Preferred are electron deficient hetaryl residues such as the nitrogen containing 6 membered rings like pyridines, pyrimidines, pyrazines or 1,3,5-triazines or its N-oxides. Most preferred are the hetaryl residues pyrimidinyl or pyrazinyl. The aryl or hetaryl rings may be substituted by one or more substituents selected from halogen, hydroxy, alkoxy, amino, dialkylamino, cyano, lower alkyl, lower alkenyl, lower alkinyl, lower acyl, lower alkylthio, lower alkylsulfonyl, lower alkylaminocarbonyl, aminocarbonyl, $SO_2NR_3R_4$, nitro, lower alkoxycarbonyl, carboxy, wherein R3 and R4, which can be the same or different represent hydrogen; C_1-C_6 alkyl, straight chained or branched, which can be substituted one or several times by OH, $N(CH_3)_2$ or which can be interrupted by oxygen, or represent CO R_5, wherein R_5 is an alkyl group which can be substituted by NH_2. Preferred are substitutions in para and/or meta position by one to two of the above listed substituents.

Lower alkyl in residue R_2 as such or in combinations with other residues denotes C_1-C_6-alkyl, preferred are methyl, ethyl, propyl, isopropyl or tert.-butyl.

Lower alkenyl denotes C_2-C_6 alkenyl, preferably allyl or pentadienyl. Lower alkinyl denotes C_2-C_6 alkinyl, preferably propargyl.

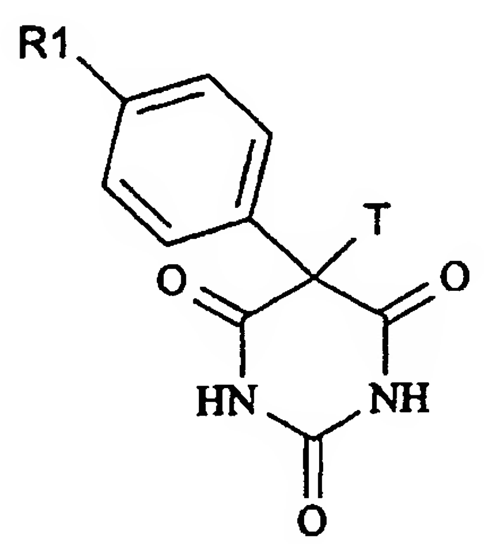
Lower acyl in the residue R_2 above all denotes -C(O)-C_1-C_6-alkyl or -C(O)H, preferred for an acetyl group.

The alkyl residues in R_2, can optionally be interrupted once or several times by heteroatoms (O, S, NH).

Halogen is understood as fluorine, chlorine, bromine, iodine, preferably chlorine or bromine.

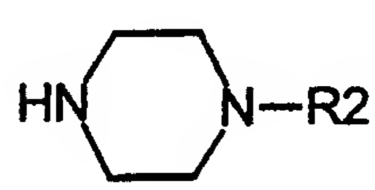
If compounds of the general formula I contain one or several asymmetric carbon atoms, the optically active compounds of the general formula I are also a subject matter of the present invention.

Compounds of the general formula I can be synthesized by well-known processes preferably in that compounds of the general formula II



(II)

in which R_1 has the above-mentioned meaning and T represents a leaving group such as Hal or OSO_2R_3. Hal denoting chlorine, bromine or iodine and R_3, denoting an aryl or a methyl residue, are reacted with a compound of the general formula III



(III)

in which R_2 has the meaning stated above and optionally converted into pharmaceutically acceptable salts.

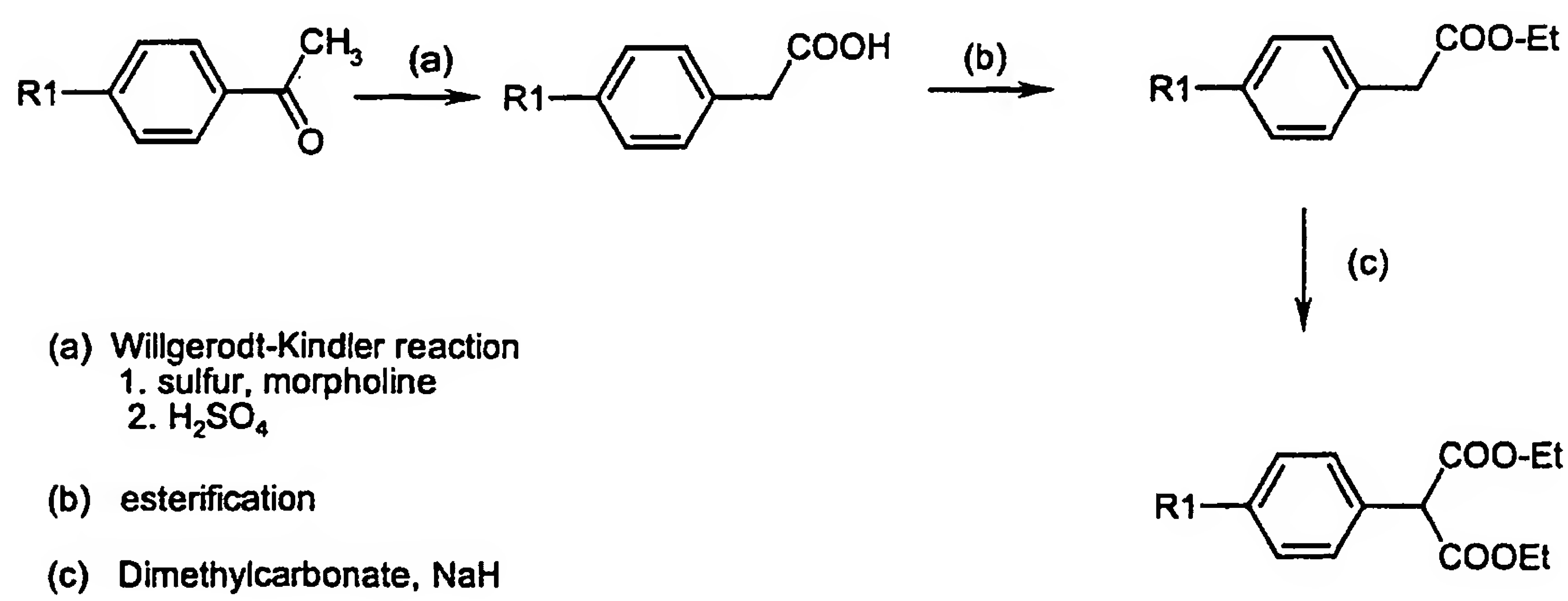
Compounds of the general formula II can be synthesized by analogy to known literature procedures. Thus for example pyrimidine-2,4,6-triones brominated in the 5-position can be synthesized by reacting the appropriate bromomalonic acid dialkyl esters with urea (e.g. Acta Chim. Acad. Sci. Hung. 107 (2), 139 (1981)). The corresponding brominated or chlorinated compounds of the general formula II can be obtained by reacting pyrimidine-2,4,6-triones substituted by R_1–Phenyl in the 5-position with bromine (analogous to J. Prakt. Chemie 136, 329 (1933) or J. Chem. Soc. 1931, 1870) or sulfuryl

chloride (J. Chem. Soc. 1938, 1622) or N-bromo-succinimide or similar brominating agents. Such procedures are also described in EP0869947.

Amines of the general formula III are commercially available or are usually known in the literature or in analogy to the described methods in the experimental part.

Pyrimidine-2,4,6-triones of formula II with T representing hydrogen can be prepared according to known methods by reacting malonic acid esters with urea (see for example J. Med. Chem. 10, 1078 (1967) or Helvetica Chim. Acta 34, 459 (1959), Pharmacie 38 (1), 65 (1983)) or EP0869947. The reactions are usually carried out in alcohols such as methanol, ethanol or butanol in the presence of an appropriate sodium alcoholate at temperatures between 40°C and 100°C

The malonic acid esters which are needed for the preparation of pyrimidine-2,4,6-triones are known from the literature or can be produced according to processes known from the literature. A convenient process for the preparation of malonic acids where R1 has the above mentioned meaning is described in the following scheme:



Examples for these reactions can be found in Houben-Weyl Vol E5/2 , J. Org. Chem. 46, 2999 (1981) and Arch. Pharm. 323, 579 (1990)

Compounds of the general formula I can contain one or several chiral centres and can then be present in a racemic or in an optically active form. The racemates can be separated according to known methods into the enantiomers. Preferably diastereomeric salts which can be separated by crystallization are formed from the racemic mixtures by

reaction with an optically active acid such as e.g. D- or L-tartaric acid, mandelic acid, malic acid, lactic acid or camphorsulfonic acid or with an optically active amine such as e.g. D- or L-α-phenyl-ethylamine, ephedrine, quinidine or cinchonidine.
Alkaline salts, earth alkaline salts like Ca or Mg salts, ammonium salts, acetates or hydrochlorides are mainly used as pharmaceutically acceptable salts which are produced in the usual manner e.g. by titrating the compounds with inorganic or organic bases or inorganic acids such as e.g. sodium hydroxide, potassium hydroxide, aqueous ammonia, C_1-C_4-alkyl-amines such as e.g. triethylamine or hydrochloric acid. The salts are usually purified by reprecipitation from water/acetone.

The new compounds of formula I and salts thereof according to the invention can be administered enterally or parenterally in a liquid or solid form. In this connection all the usual forms of administration come into consideration such as for example tablets, capsules, coated tablets, syrups, solutions, suspension etc. Water which contains additives such as stabilizers, solubilizers and buffers that are usual in injection solutions is preferably used as the injection medium.

Such additives are e.g. tartrate and citrate buffer, ethanol, complexing agents (such a ethylenediaminetetra-acetic acid and non-toxic salts thereof), high-molecular polymers (such as liquid polyethylene oxide) to regulate viscosity. Liquid carrier substances for injection solutions have to be sterile and are preferably dispensed into ampoules. Solid carrier substances are e.g. starch, lactose, mannitol, methylcellulose, talcum, highly dispersed silicic acids, higher molecular fatty acids (such as stearic acid), gelatins, agar-agar, calcium phosphate, magnesium stearate, animal and vegetable fats, solid high-molecular polymers (such as polyethylene glycols); suitable preparations for oral application can optionally also contain flavourings and sweeteners.

The dosage depends on various factors such as manner of administration, species, age and/or individual state of health. The doses to be administered daily are about 10-1000 mg/human, preferably 100-500 mg/human and can be taken singly or distributed over several administrations.

Prodrugs of the compounds of the invention are such which are converted in vivo to the pharmacological active compound. The most common prodrugs are carboxylic acid esters.

Example 1

5-(4-(4-Chloro-phenoxy)-phenyl)-5-(4-pyrimidine-2-yl-piperazine)-pyrimidine-2,4,6-trione

A) 1-(4-(4-Chloro-phenoxy)-phenyl-ethanone

4-Fluoro-acetophenone (24.4 g) is dissolved in dimethylformamide (180ml), 4-Chlorophenol (22.8 g) and potassium carbonate (29.5 g) are added . The mixture is heated with stirring for 7 hrs. under reflux. After cooling the mixture is diluted with water and extracted with methylene chloride. The organic phase is washed with water, dried and evaporated to yield 38 g of a crystalline solid. M.p.66-68 °C.

B) 2-(4-(4-Chloro-phenoxy)-phenyl)-morpholine-4-yl-ethanthione

12.4 g of the product obtained by the above procedure are mixed with sulfur (4 g) and morpholine (8.8 ml). The mixture is heated to 150 °C for 2 hrs, cooled in an ice bath and treated with ethanol(20 ml) for 30 minutes. The precipitated crystals are collected and recrystallized from ethanol to yield 13 g of the title compound. M.p. 104-105 °C.

C) (4-(4-Chloro-phenoxy)-phenyl)-acetic acid

10.4 g of the compound prepared in step B are heated together with 50% sulfuric acid (200 ml) to 130 °C for 8 hrs. After cooling to room temperature, the reaction mixture is diluted with water (300 ml) and extracted with ethyl acetate. The organic phase is washed with water and subsequently extracted with 2N sodium carbonate solution. The aqueous phase is acidified with dilute hydrochloric acid, ethyl acetate is added, the organic phase is separated, dried and evaporated to yield 5.1 g of a brownish residue. m.p.98-100 °C.

D) (4-(4-Chloro-phenoxy)-phenyl)-acetic acid methyl ester

5.1 g of the product from step C are dissolved in methanol (50 ml). The solution is cooled to –10 °C and treated with thionyl chloride (3 ml) and subsequently heated under reflux for 1 hour. The reaction mixture is evaporated and the residue dissolved in ether. The ether phase is washed with water, dried and evaporated to yield 5.1 g of a reddish brown oil.

E) 2-(4-(4-Chloro-phenoxy)-phenyl)-malonic acid dimethyl ester

A suspension of sodium hydride (350 mg) in dimethyl carbonate (10 ml) is treated at room temperature with the product obtained in step D. The mixture is heated to 90 °C for 1 hour, cooled and poured into ice water and extracted with methylene chloride. The extract is dried and evaporated to yield 5.7 of the title compound as an oil.

F) 5-(4-(4-Chloro-phenoxy)-phenyl)-pyrimidine,2,4,-6-trione

Sodium (800 mg) is dissolved in ethanol (80 ml). To this solution is added urea (1.65 g) and a solution of the compound obtained above in ethanol (5.5 g). The mixture is heated for 3 hours under reflux, cooled to room temperature, treated with ice water (100 ml) and acidified with dilute hydrochloric acid. The precipitate is collected, washed with water and dried to yield 5g of the title compound. M.p. 257-258 °C.

G) 5-Bromo 5-(4-(4-Chloro-phenoxy)-phenyl)-pyrimidine,2,4,-6-trione

A suspension of the compound obtained in step F (6.3 g), N-bromo-succinimide (4.1 g) and dibenzoylperoxide (100 mg) in carbon tetrachloride (120 ml) is stirred for 3 hours at room temperature. The mixture is evaporated , the residue extracted with ethyl acetate. The organic phase is dried and evaporated to yield 7.5 g of the title compound as a thick oil.

H) 5-(4-(4-Chloro-phenoxy)-phenyl)-5-(4-pyrimidine-2-yl-piperazine)-pyrimidine-2,4,6-trione

A solution of the compound from step G (410 mg) in methanol (5 ml) is treated with N-(pyrimidin-2-yl)-piperazin (330 mg). The mixture is stirred for 24 hours.The residue obtained after evaporation of the reaction mixture is chromatographed on silica gel with methylenchloride/methanol 5% as eluent. Pooling of the relevant fractions yields 410 mg of the title compound as an amorphous solid identified by mass spectroscopy: m/e 492.

Example 2

5-[4-(4-Chloro-phenoxy)-phenyl]-5-(2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)-pyrimidine-2,4,6-trione

The title compound was prepared by analogy to example 1 step H using 330 mg 1-(pyrazin-2-yl)-piperazine instead of the N-(pyrimidin-2-yl)-piperazine yielding 460 mg of the title compound as an amorphous product identified by mass spectrometry: m/e : 492

Example 3

The following compounds were prepared using the procedures of example 1 replacing 4-chlorophenol by the corresponding phenols. The final products were identified by mass spectrometry

No.	Chemical name	m/e
1	5-[4-(3,4-Dichloro-phenoxy)-phenyl]-5-(4-pyrimidin-2-yl-piperazin-1-yl)-pyrimidine-2,4,6-trione	526
2	5-[4-(3,4-Dichloro-phenoxy)-phenyl]-5-(2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)-pyrimidine-2,4,6-trione	526
3	5-[4-(2,4-Dichloro-phenoxy)-phenyl]-5-(4-pyrimidin-2-yl-piperazin-1-yl)-pyrimidine-2,4,6-trione	526
4	5-[4-(2,4-Dichloro-phenoxy)-phenyl]-5-(2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)-pyrimidine-2,4,6-trione	526
5	5-[4-(2-Chloro-phenoxy)-phenyl]-5-(4-pyrimidin-2-yl-piperazin-1-yl)-pyrimidine-2,4,6-trione	492
6	5-[4-(2-Chloro-phenoxy)-phenyl]-5-(2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)-pyrimidine-2,4,6-trione	492
7	5-[4-(Phenoxy)-phenyl]-5-(4-pyrimidin-2-yl-piperazin-1-yl)-pyrimidine-2,4,6-trione	458
8	5-[4-(Phenoxy)-phenyl]-5-(2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)-pyrimidine-2,4,6-trione	458
9	5-[4-(4-Methyl-phenoxy)-phenyl]-5-(4-pyrimidin-2-yl-piperazin-1-yl)-pyrimidine-2,4,6-trione	472

10	5-[4-(4-Methyl-phenoxy)-phenyl]-5-(2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)-pyrimidine-2,4,6-trione	472
11	5-[4-(4-*tert*-Butyl-phenoxy)-phenyl]-5-(4-pyrimidin-2-yl-piperazin-1-yl)-pyrimidine-2,4,6-trione	514
12	5-[4-(4-*tert*-Butyl-phenoxy)-phenyl]-5-(2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)-pyrimidine-2,4,6-trione	514
13	5-[4-(3,4-Dimethyl-phenoxy)-phenyl]-5-(4-pyrimidin-2-yl-piperazin-1-yl)-pyrimidine-2,4,6-trione	486
14	5-[4-(3,4-Dimethyl-phenoxy)-phenyl]-5-(2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)-pyrimidine-2,4,6-trione	486
15	5-[4-(4-Bromo-phenoxy)-phenyl]-5-(4-pyrimidin-2-yl-piperazin-1-yl)-pyrimidine-2,4,6-trione	537
16	5-[4-(4-Bromo-phenoxy)-phenyl]-5-(2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)-pyrimidine-2,4,6-trione	537

Example 4

4-(4-5-[4-(4-Chloro-phenoxy)-phenyl]-2,4,6-trioxo-hexahydro-pyrimidin-5-yl-piperazin-1-yl)-N-(2-hydroxy-ethyl)-benzenesulfonamide

A) *N*-(2-Hydroxy-ethyl)-4-piperazin-1-yl-benzenesulfonamide

4-Fluoro-benzenesulfonylchloride is dissolved in dichloromethane (20 ml) and treated with a solution of ethanolamine (1.2 ml) in dichloromethane (10 ml). The mixture is stirred for 1 hour and extracted twice with water (50 ml). The water phase is saturated with sodium chloride and extracted twice with ethyl acetate. The combined organic phases are dried with magnesium sulfate and evaporated. 1.4 g of the resulting 4-fluoro-N-hydroxyethyl-benzenesulfonamide are dissolved in water (15 ml) and treated with piperazine (2.6 g). The mixture is refluxed for 6 hrs and kept at room temperature for 24 hrs. The precipitate is collected, washed with little water and dried to yield 1.6 g of the title compound identified by mass spectrometry (APCI [M+H] = 286

B) 4-(4-5-[4-(4-Chloro-phenoxy)-phenyl]-2,4,6-trioxo-hexahydro-pyrimidin-5-yl-piperazin-1-yl)-N-(2-hydroxy-ethyl)-benzenesulfonamide

A solution of the compound from example 1 procedure G (230 mg) in methanol (5 ml) is treated with *N*-(2-Hydroxy-ethyl)-4-piperazin-1-yl-benzenesulfonamide (330 mg) (see above) The mixture is stirred for 24 hours. The residue obtained after evaporation of the reaction mixture is chromatographed on silica gel with methylenchloride/methanol (15%) as eluent. Pooling of the relevant fractions yields 186 mg of the title compound as an amorphous solid identified by mass spectroscopy: APCI [M+1]=614.

Example 5

The following compounds are prepared using the procedures of example 1 substituting 4-chlorophenol with the corresponding phenols where needed. The piperazinederivatives are prepared according to example 4 procedure A and exchanging ethanolamine with the appropriate amine. The final products are identified by mass spectrometry.

No.	Name	MS results APCI [M+H]
1	4-4-[2,4,6-Trioxo-5-(4-phenoxy-phenyl)-hexahydro-pyrimidin-5-yl]-piperazin-1-yl-benzenesulfonamide	536
2	4-4-[5-(4-Butoxy-phenyl)-2,4,6-trioxo-hexahydro-pyrimidin-5-yl]-piperazin-1-yl-benzenesulfonamide	516
3	4-[4-(5-Biphenyl-4-yl-2,4,6-trioxo-hexahydro-pyrimidin-5-yl)-piperazin-1-yl]-benzenesulfonamide	520
4	N-(2-Hydroxy-ethyl)-4-4-[2,4,6-trioxo-5-(4-phenoxy-phenyl)-hexahydro-pyrimidin-5-yl]-piperazin-1-yl-benzenesulfonamide	580
5	N,N-Bis-(2-hydroxy-ethyl)-4-4-[2,4,6-trioxo-5-(4-phenoxy-phenyl)-hexahydro-pyrimidin-5-yl]-piperazin-1-yl-benzenesulfonamide	624
6	4-(4-5-[4-(4-Bromo-phenoxy)-phenyl]-2,4,6-trioxo-hexahydro-pyrimidin-5-yl-piperazin-1-yl)-benzenesulfonamide	615
7	4-(4-5-[4-(4-Bromo-phenoxy)-phenyl]-2,4,6-trioxo-hexahydro-pyrimidin-5-yl-piperazin-1-yl)-N-(2-dimethylamino-ethyl)-benzenesulfonamide	686
8	N-(2-Dimethylamino-ethyl)-4-[4-(5-octyl-2,4,6-trioxo-hexahydro-pyrimidin-5-yl)-piperazin-1-yl]-benzenesulfonamide	551
9	4-(4-5-[4-(4-Chloro-phenoxy)-phenyl]-2,4,6-trioxo-hexahydro-pyrimidin-5-yl-piperazin-1-yl)-benzenesulfonamide	570

10	4-(4-5-[4-(4-Chloro-phenoxy)-phenyl]-2,4,6-trioxo-hexahydro-pyrimidin-5-yl-piperazin-1-yl)-N,N-bis-(2-hydroxy-ethyl)-benzenesulfonamide	658
11	N-(2,3-Dihydroxy-propyl)-4-4-[2,4,6-trioxo-5-(4-phenoxy-phenyl)-hexahydro-pyrimidin-5-yl]-piperazin-1-yl-benzenesulfonamide	610
12	N-(2-Hydroxy-1-hydroxymethyl-ethyl)-4-4-[2,4,6-trioxo-5-(4-phenoxy-phenyl)-hexahydro-pyrimidin-5-yl]-piperazin-1-yl-benzenesulfonamide	610
13	N-2-[2-(2-Hydroxy-ethoxy)-ethoxy]-ethyl-4-4-[2,4,6-trioxo-5-(4-phenoxy-phenyl)-hexahydro-pyrimidin-5-yl]-piperazin-1-yl-benzenesulfonamide	668
14	4-(4-5-[4-(4-Chloro-phenoxy)-phenyl]-2,4,6-trioxo-hexahydro-pyrimidin-5-yl-piperazin-1-yl)-N-(2,3-dihydroxy-propyl)-benzenesulfonamide	644
15	4-(4-5-[4-(4-Chloro-phenoxy)-phenyl]-2,4,6-trioxo-hexahydro-pyrimidin-5-yl-piperazin-1-yl)-N-(2-hydroxy-1-hydroxymethyl-ethyl)-benzenesulfonamide	644
16	4-(4-5-[4-(4-Chloro-phenoxy)-phenyl]-2,4,6-trioxo-hexahydro-pyrimidin-5-yl-piperazin-1-yl)-N-[2-(2-hydroxy-ethoxy)-ethyl]-benzenesulfonamide	658
17	4-(4-5-[4-(4-Chloro-phenoxy)-phenyl]-2,4,6-trioxo-hexahydro-pyrimidin-5-yl-piperazin-1-yl)-N-2-[2-(2-hydroxy-ethoxy)-ethoxy]-ethyl-benzenesulfonamide	702
18	N-(2-Hydroxy-1,1-bis-hydroxymethyl-ethyl)-4-4-[2,4,6-trioxo-5-(4-phenoxy-phenyl)-hexahydro-pyrimidin-5-yl]-piperazin-1-yl-benzenesulfonamide	640
19	4-(4-5-[4-(4-Chloro-phenoxy)-phenyl]-2,4,6-trioxo-hexahydro-pyrimidin-5-yl-piperazin-1-yl)-N-(2-hydroxy-1,1-bis-hydroxymethyl-ethyl)-benzenesulfonamide	674

Example 6

N-(2-Oxo-[1,3]dioxolan-4-ylmethyl)-4-4-[2,4,6-trioxo-5-(4-phenoxy-phenyl)-hexahydro-pyrimidin-5-yl]-piperazin-1-yl-benzenesulfonamide

The product of example 5, no. 11 (120 mg) is dissolved in a mixture of dichloromethane (5 ml) and tetrahydrofurane (5 ml). The solution is treated with N,N'-carbonyl-diimidazole (65 mg) and stirred for 4 hrs. at room temperature. The solvent is evaporated and the residue chromatographed on silica gel using dichloro-methane/methanol (9:1) as elution solvent. Evaporation of the product containing fractions yielded 60 mg of the title compound. mass spectrum: APCI [M+H] = 636, [M-H] = 634

Example 7

N-(4-Amino-butyryl)-4-4-[2,4,6-trioxo-5-(4-phenoxy-phenyl)-hexahydro-pyrimidin-5-yl]-piperazin-1-yl-benzenesulfonamide

A) 4-(4-Benzyl-piperazin-1-yl)-benzenesulfonamide

4-Fluorobenzenesulfonylchloride (25 g) are dissolved in dichloromethane (250 ml) and treated at 0 °C with an aqueous solution of ammonia (25%, 50 ml). The mixture is stirred for 2 hrs. with cooling and overnight at room temperature. The reaction mixture is acidified and the organic solvent evaporated. The residue is extracted with ethyl acetate to yield 20 g 4-fluorobenzenesulfonamide, which is dissolved in water (300 ml), treated with 1-benzyl-piperazine (102 g) and refluxed for 24 hrs. The reaction mixture is filtered to yield 26 g of the title compound. (mass spec APCI [M+H] = 332)

B) 4-[4-(Piperazin-1-yl)-benzenesulfonylamino]-4-oxo-butyl-carbamic acid tert-butyl ester

4-(N-tert.-Butoxycarbonyl)-aminobutyric acid (3.05 g) is dissolved in tetrahydrofurane (30 ml) and treated with N,N'-carbonyldiimidazol (2.5 g). The mixture is stirred at room temperature for 15 min, heated under reflux for 15 min and stirred for 1 hour at room temperature. The product from step A (3.3 g) is added and the mixture is stirred overnight.. The solvent is evaporated and the residue mixed with dichloromethane and water. The organic phase is separated, dried and the solvent evaporated. The residue is chromatographed on silica gel using dichloromethane/methanol (9:1) as eluting solvent. The product is subjected to catalytic hydrogenation in methanol using Pd on carbon to yield 2.5 g of the title compound. (mass spec APCI [M-H] = 425).

C) N-(4-Amino-butyryl)-4-4-[2,4,6-trioxo-5-(4-phenoxy-phenyl)-hexahydro-pyrimidin-5-yl]-piperazin-1-yl-benzenesulfonamide

The product obtained in procedure B is reacted analogously to example 1 procedure H with 5-bromo 5-(4-(phenoxy)-phenyl)-pyrimidine-2,4,6-trione. The latter compound is prepared analogously to the procedures described in example 1 substituting the p-chlorophenol with phenol. To remove the BOC-protecting group the product (290 mg) is dissolved in a 4 N solution of HCl in dioxane. After 1 hour at room temperature the solution is decanted and the residue triturated with ether to yield 180 mg of the title compound. (mass spectrum APCI [M+H] = 621).

Example 8

The following compounds are prepared using the procedures of example 7 substituting 4-(N-tert.butoxycarbonyl)-amino-butyric acid with the appropriate N-tert.butoxycarbonyl protected amino acid. The final products were identified by mass spectrometry.

No.	Name	MS results APCI [M+H]
1	N-Aminoacetyl-4-4-[2,4,6-trioxo-5-(4-phenoxy-phenyl)-hexahydro-pyrimidin-5-yl]-piperazin-1-yl-benzenesulfonamide	593
2	N-(5-Amino-pentanoyl)-4-4-[2,4,6-trioxo-5-(4-phenoxy-phenyl)-hexahydro-pyrimidin-5-yl]-piperazin-1-yl-benzenesulfonamide	635
3	N-(5-Amino-pentanoyl)-4-(4-5-[4-(4-chloro-phenoxy)-phenyl]-2,4,6-trioxo-hexahydro-pyrimidin-5-yl-piperazin-1-yl)-benzenesulfonamide	669
4	N-(4-Amino-butyryl)-4-(4-5-[4-(4-chloro-phenoxy)-phenyl]-2,4,6-trioxo-hexahydro-pyrimidin-5-yl-piperazin-1-yl)-benzenesulfonamide	655

Example 9

2-Oxo-2-(4-4-[2,4,6-trioxo-5-(4-phenoxy-phenyl)-hexahydro-pyrimidin-5-yl]-piperazin-1-yl-benzenesulfonylamino)-ethyl]-carbamic acid 4-methoxy-phenyl ester

The product of example 5 no. 1 (140 mg) is dissolved in dichloromethane (10 ml), mixed with triethylamine (0.14 ml) and treated with 4-methoxyphenylchloroformate. The mixture is stirred for 90 min at room temperature and evaporated. The residue is chromatographed on silica gel using dichloromethane/methanol (9:1) as eluent. Pooling of the relevant fractions yielded 90 mg of the title compound. (Mass spec APCI [M+H] = 743).

Example 10

In order to determine the inhibition of MMPs, for example HNC (MMP-8), the catalytic domain (isolation and purification see for example Schnierer, S., Kleine, T., Gote, T., Hillemann, A., Knäuper, V., Tschesche, H.,Biochem. Biophys. Res. Commun. (1993) 191, 319-326) is incubated with inhibitors having various concentrations. Subsequently, the initial reaction rate in the conversion of a standard substrate is measured in a manner analogous to Grams F. et al., FEBS 335 (1993) 76-80).
The results are evaluated by plotting the reciprocal reaction rate against the concentration of the inhibitor. The inhibition constant (Ki) is obtained as the negative section of the abscissis by the graphical method according to Dixon, M., Biochem. J. (1953) 55, 170-202.

The synthetic collagenase substrate is a heptapeptide which is coupled, at the C terminus, with DNP (dinitrophenol). Said DNP residue quenches by steric hindrance the fluorescence of the adjacent tryptophane of the heptapeptide. After cleavage of a tripeptide which includes the DNP group, the tryptophane fluorescence increases. The proteolytic cleavage of the substrate therefore can be measured by the fluorescence value.

a) First method

The assay was performed at 25 °C in a freshly prepared 50 mM Tris buffer (pH 8.0) treated with dithiozone to remove traces of heavy metals. 4 mM $CaCl_2$ was added and the buffer saturated wtih argon. Stock solutions of adamalysin II were prepared by centrifugation of the protein from an ammonium sulfate suspension and subsequent dissolution in the assay buffer. Stock solutions of collagenase were diluted with the assay buffer. Enzyme concentrations were determined by uv measurements ($\varepsilon_{280} = 2.8$ 10^4 $M^{-}1$ cm^{-1}, ε_{288}: 2.2 10^4 M^{-1} . cm^{-1}) and the stock solutions were stored in the cold. This solution was diluted 1:100 to obtain the final 16 nM assay concentration. The fluorogenic substrate DNP-Pro-Leu-Gly-Leu-Trp-Ala-D-Arg-NH_2 with a K_m of 52 µM was used at a concentration of 21.4 µM; for the K_i determination a 12.8 µM concentration has also been used. Substrate fluorescence was measured at an excitation and emission wavelength of λ = 320 and 420 nm, respectively, on a spectrofluorimeter (Perkin Elmer, Model 650-40) equipped with a thermostated cell holder. Substrate hydrolysis was monitored for 10 min. immediately after adding the enzyme. All reactions were performed at least in triplicate. The K_i values-of the inhibitors were calculated from the intersection point of the straight lines obtained by the plots of v_o/v_i vs. [concentration of inhibitor], whereas IC_{50} values were calculated from plots of v_i/v_o [concentration of inhibitor] by non-linear regression with simple robust weighting.

b) Second method

Assay buffer:
50 mM Tris/HCI pH 7.6 (Tris= Tris-(hydroxymethyl)-aminomethan)
100 mM NaCl/10 mM CaC12/5 % MeOH (ff necessary)
Enzyme: 8 nM catalytic domain (Met80-Gly242) of human neutrophil collagenase (MMP-8)

Substrate: 10 microM DNP-Pro-Leu-Gly-Leu-Trp-Ala-D-Arg-NH2
Total assay volume: 1 ml

A solution of the enzyme and inhibitor in assay buffer (25 °C) was prepared. The reaction was started by giving the substrate into the solution. The cleavage of the fluorogenic substrate was followed by fluorescence spectroscopy with an excitation and emission wavelength of 280 and 350 nm, respectively. The IC_{50} value was calculated as

the inhibitor concentration, which is necessary to decrease the velocity of the reaction to the half in comparison to the reaction without inhibitor.

Table 1 shows the IC_{50} values found in comparison with the compounds from example 26 and preferred compound no. 118 cited in the patent application EP0869947

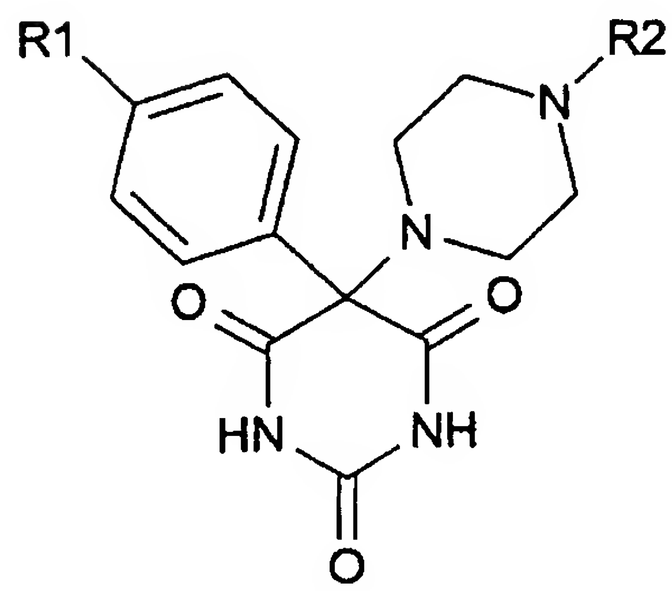
Table 1: IC_{50} Values of MMP-Inhibitor (vs. MMP-8, catalytic domain)

Reference Compound from EP0869947	**IC_{50} [nM]**
preferred no. 118	60
example 26	15

Compounds from this invention	**IC_{50} [nM]**
Example 1	10
Example 2	4
Example 3 – no. 1	4
Example 3 – no. 2	2
Example 3 – no. 15	4
Example 3 – no. 15	4
Example 4	10
Example 5 – no. 6	2.8
Example 5 – no. 7	13
Example 5 – no. 9	12
Example 5 – no. 10	9
Example 5 – no. 11	4.5
Example 5 – no. 12	5.5
Example 5 – no. 13	6
Example 5 – no. 18	13
Example 5 – no. 19	9
Example 6	9

Patent claims

1. Compounds of formula



(I)

in which

R_1 represents a phenyl, phenoxy , phenylthio, phenylsulfinyl, phenylsulfonyl, phenylamino or phenylmethyl residue, wherein the phenyl moiety can be substituted by one or more halogen atoms, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkyl, cyano or nitro groups, and

R_2 represents an optionally substituted aryl or heteroaryl group, as well as their pharmaceutically acceptable salts or prodrugs of the compounds of formula I.

2. Compounds of formula I according to claim 1 wherein R_1 is phenoxy,

3. Compounds of formula I according to claim 1 wherein R_1 is phenoxy substituted one or more times by chlorine, bromine, methyl or tert. butyl,

4. Compounds of formula I according to claim 1, wherein R_2 is pyrimidine, pyrazine or its N-oxides.

5. Compounds of formula I according to claim 1 wherein R_2 is phenyl substituted by $-SO_2NR_3R_4$, wherein R3 and R4, are the same or different, and represent hydrogen; C_1-C_6 alkyl, straight chained or branched, which can be substituted one or several times by OH, $N(CH_3)_2$ or which can be interrupted by oxygen, or represent CO R_5, wherein R_5 is an alkyl group which can be substituted by NH_2.

6. Compound of formula I according to claim5 whereby R_3 represent hydrogen and R_4 represents hydrogen, $-CH_2CH_2OH$; $-CH_2CH_2-N(CH_3)_2$; $-CH_2-CH(OH)-CH_2OH$; $-CH-(CH_2OH)_2$; $-CH_2-CH_2-O-CH_2CH_2-O-CH_2CH_2OH$; or $-C(CH_2OH)_3$.

7. Compounds of formula I according to claim 1 selected from the group consisting of:

5-(4-(4-Chloro-phenoxy)-phenyl)-5-(4-pyrimidine-2-yl-piperazine)-pyrimidine-2,4,6-trione

5-[4-(4-Chloro-phenoxy)-phenyl]-5-(2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)-pyrimidine-2,4,6-trione

5-[4-(3,4-Dichloro-phenoxy)-phenyl]-5-(4-pyrimidin-2-yl-piperazin-1-yl)-pyrimidine-2,4,6-trione

5-[4-(3,4-Dichloro-phenoxy)-phenyl]-5-(2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)-pyrimidine-2,4,6-trione

5-[4-(4-Bromo-phenoxy)-phenyl]-5-(4-pyrimidin-2-yl-piperazin-1-yl)-pyrimidine-2,4,6-trione

4-(4-5-[4-(4-Chloro-phenoxy)-phenyl]-2,4,6-trioxo-hexahydro-pyrimidin-5-yl-piperazin-1-yl)-N-(2-hydroxy-ethyl)-benzenesulfonamide

4-(4-5-[4-(4-Bromo-phenoxy)-phenyl]-2,4,6-trioxo-hexahydro-pyrimidin-5-yl-piperazin-1-yl)-benzenesulfonamide

4-(4-5-[4-(4-Bromo-phenoxy)-phenyl]-2,4,6-trioxo-hexahydro-pyrimidin-5-yl-piperazin-1-yl)-N-(2-dimethylamino-ethyl)-benzenesulfonamide

4-(4-5-[4-(4-Chloro-phenoxy)-phenyl]-2,4,6-trioxo-hexahydro-pyrimidin-5-yl-piperazin-1-yl)-benzenesulfonamide

4-(4-5-[4-(4-Chloro-phenoxy)-phenyl]-2,4,6-trioxo-hexahydro-pyrimidin-5-yl-piperazin-1-yl)-N,N-bis-(2-hydroxy-ethyl)-benzenesulfonamide

N-(2,3-Dihydroxy-propyl)-4-4-[2,4,6-trioxo-5-(4-phenoxy-phenyl)-hexahydro-pyrimidin-5-yl]-piperazin-1-yl-benzenesulfonamide

N-(2-Hydroxy-1-hydroxymethyl-ethyl)-4-4-[2,4,6-trioxo-5-(4-phenoxy-phenyl)-hexahydro-pyrimidin-5-yl]-piperazin-1-yl-benzenesulfonamide

N-2-[2-(2-Hydroxy-ethoxy)-ethoxy]-ethyl-4-4-[2,4,6-trioxo-5-(4-phenoxy-phenyl)-hexahydro-pyrimidin-5-yl]-piperazin-1-yl-benzenesulfonamide

N-(2-Hydroxy-1,1-bis-hydroxymethyl-ethyl)-4-4-[2,4,6-trioxo-5-(4-phenoxy-phenyl)-hexahydro-pyrimidin-5-yl]-piperazin-1-yl-benzenesulfonamide

4-(4-5-[4-(4-Chloro-phenoxy)-phenyl]-2,4,6-trioxo-hexahydro-pyrimidin-5-yl-piperazin-1-yl)-N-(2-hydroxy-1,1-bis-hydroxymethyl-ethyl)-benzenesulfonamide

N-(2-Oxo-[1,3]dioxolan-4-ylmethyl)-4-4-[2,4,6-trioxo-5-(4-phenoxy-phenyl)-hexahydro-pyrimidin-5-yl]-piperazin-1-yl-benzenesulfonamide

8. Pharmaceutical compositions containing as active ingredient a compound according to claims 1 to 7 in admixture with pharmaceutically acceptable excipients or diluents.

9. Use of compounds according to claims 1 to 7 for the preparation of a medicament having metallo-proteinase inhibitor activity.

10. Use of compounds according to claim 9 having antitumor and/or antimetastatic activity.

INTERNATIONAL SEARCH REPORT

Intern   nal Application No
PCT/EP 00/09535

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/545 C07D405/12 A61K31/515

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 97 23465 A (BOEHRINGER MANNHEIM GMBH ;BOSIES ELMAR (DE); ESSWEIN ANGELIKA (DE)) 3 July 1997 (1997-07-03) cited in the application see claim 1 definitions and page 5, lines 24, page 6, lines 11 page 7, lines 6-12 and page 7, lines 21-35 and claims 4-6	1-10
A	DE 12 46 743 B (VEB ARZNEIMITTELWERK DRESDEN) 10 August 1967 (1967-08-10) the whole document	1-10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
22 November 2000	28/11/2000

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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A	CHEMICAL ABSTRACTS, vol. 98, no. 1, 1983 Columbus, Ohio, US; abstract no. 375z, KNABE,J: "Derivatives of barbituric acids" XP002026400 abstract	1-10
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern   ıal Application No
PCT/EP 00/09535

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			CN 1251312	A	26-04-2000
			JP 2000095708	A	04-04-2000
			NO 994583	A	23-03-2000
			PL 335592	A	27-03-2000
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			ZA 9610765	A	17-07-1998
DE 1246743	B		NONE		

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